Journal of Medical Virology 59:221–226 (1999)

Comparison of Respiratory Syncytial Virus Humoral Immunity and Response to Infection in Young and Elderly Adults

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Little information about immunity to respiratory syncytial virus (RSV) and disease pathogenesis in elderly persons exists. Humoral immunity to RSV was assessed in 41 young, 56 healthy elderly, and 49 frail elderly adults by measuring baseline RSV specific IgG by enzyme immunoassay (EIA) and microneutralization assay (MNA) in serum. A comparison of the immune response of 11 young and 28 elderly persons with natural RSV infection was also performed. Despite significant differences in age and functional status, no decreases in RSV antibody levels by either EIA or MNA were noted in the elderly compared with the young. Mean baseline MNA titers expressed as log2 were 10.5 ± 1.1 for the young, 10.5 ± 1.5 for the healthy elderly, and 10.9 ± 1.6 for the frail elderly. The frail elderly who attend a daycare had the highest RSV titers to F by EIA at 16.6 ± 2.0, compared with 15.4 ± 1.4 and 15.1 ± 1.4 in the healthy elderly and young, respectively. This finding may reflect recent infection due to their communal setting or increased production of non-neutralizing antibody. The immune response of older persons to RSV infection was as vigorous as the younger subjects, with 79% having a ≥fourfold rise in MNA titers compared to 64% in the young. These data suggest that the severe clinical manifestations of RSV in the elderly are not due to a significant defect in humoral immunity. ***J. Med. Virol. 59: 221–226, 1999.***

KEY WORDS: respiratory syncytial virus; elderly; immunity; antibody

INTRODUCTION

Respiratory syncytial virus (RSV), the most important cause of lower respiratory tract disease in young children, is now also recognized as a significant viral pathogen in elderly and frail adults [Mathur et al., 1980; Spelman and Stanley, 1983; Dowell et al., 1996]. RSV causes excess morbidity and mortality in persons older than 65 years of age, both in the community and in nursing homes, at rates second only to influenza [Fleming and Cross, 1993; Falsey et al., 1995a]. Although generally less severe, reinfections with RSV are common and occur throughout life, indicating that natural infection induces only partial immunity. At present, there are no unequivocal correlates of immunity in humans; however, animal data indicate that antibody to the two surface proteins, the attachment protein (G) and the fusion protein (F), is protective [Walsh et al., 1987]. In addition, serum-neutralizing titers have been shown to correlate inversely with risk of primary infection in children and reinfection in children and young healthy adults [Glezen et al., 1981, 1986; Hall et al., 1991]. In contrast to infants, there are few published data on immunity in the elderly. It is not known if all older persons or only specific groups, such as the frail elderly, have diminished humoral immunity. If correlates of immunity, such as specific protective neutralizing antibody titer, could be established, then screening of various adult populations would provide an estimate of the number of individuals at risk for infection. This information would be useful in targeting groups for vaccination.

In a preliminary investigation of humoral immunity in adults, RSV serum neutralizing titers in 20 healthy older adults were significantly lower and demonstrated greater diversity than younger subjects [Falsey, 1998]. The purpose of the current study was to confirm and extend these findings by measuring baseline RSV an-

Grant sponsor: National Institute of Aging; Grant number: P60-AG10463-06.

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Accepted 27 January 1999

tibody titers in a larger number of young and elderly subjects. Possible confounding variables such as nutritional and functional status on RSV immunity were evaluated. Finally, we compared the humoral immune response to natural RSV infection in frail older persons to the response in healthy young persons.

MATERIALS AND METHODS

Subjects

Approximately 50 volunteers were recruited from each of three groups for a one-time cross-sectional study in October 1996 in Rochester, New York. Informed consent was obtained from all volunteers or their legal guardians prior to enrollment in the study. Age and functional status defined the three cohorts. The first group consisted of young, healthy persons under age 50 and was recruited from the hospital and adult daycare center staff. The second group was healthy, older persons and was defined as individuals over age 60, living independently in the community. The third group consisted of frail, older persons over age 65 attending an adult daycare program. These individuals were nursing home eligible by New York Medicaid standards but were maintained in the community by extensive home services and attendance at the daycare centers. Subjects were excluded if they had metastatic malignancy, uremia, hepatic failure, chronic infection, or inflammatory diseases or used immunosuppressive drugs. Demographic information and a medical history were recorded. The functional status of each subject was determined using standard assessment tools, including the Katz activities of daily living scale (ADL), and the Lawton scale of instrumental activities of daily living (IADL). A score of 0 indicated total independence and a score of 12 defined total dependence. The same project nurse performed all assessments, and blood for immunologic and nutritional assays was collected from volunteers at enrollment.

Serum obtained from the volunteers in the cross-sectional study as well as the baseline and convalescent specimens from RSV-infected subjects were then analyzed for RSV antibodies by enzyme immunoassay (EIA) and microneutralization assay (MNA). In addition, a random subset of subjects had serum neutralization tests performed with and without complement to evaluate possible age-related changes in immunoglobulin G (IgG) isotypes. All subjects in the cross-sectional diversity study had serum albumin, and vitamins A, C, E, and B12 measured.

The entire daycare staff and approximately 90% of the 240 elderly daycare attendees also participated in a respiratory infections surveillance project, which began in January 1992 and ran through April 1998 [Falsey et al., 1995b]. During that period, 11 staff members and 28 elderly persons were documented to have RSV infection by culture or serology and had baseline and convalescent sera available for analysis. RSV infection was defined as a ≥fourfold rise in RSV-specific IgG by EIA. These individuals were used to compare age-related humoral responses to natural RSV infection.

Laboratory Methods

Enzyme immunoassay (EIA-F, EIA-G_A, EIA-G_B). EIA was used for measurement of serum IgG to purified RSV envelope glycoproteins from group A and B viruses [Falsey and Walsh, 1997a]. The RSV fusion (F) protein and the attachment protein from the Long strain of RSV (G_A) and the attachment protein of the 18537 strain of RSV (G_B) were purified by affinity chromatography with F and G specific monoclonal antibodies (MAb) according to published methods [Walsh et al., 1985, 1986]. Antigens were diluted in bicarbonate buffer and coated onto 96-well enzyme-linked immunosorbent assay (ELISA) plates (Immunlon-1, Dynex Technologies Inc., Chantilly, VA) overnight at 4°C. Serum samples (serially diluted from 1:800 to 1:102,400) were incubated overnight in duplicate wells at 37°C. After washing, bound IgG was detected by a 3-hr incubation with alkaline phosphatase-conjugated goat anti-human IgG, followed by washing and addition of substrate. The titer was defined as the highest dilution with an optical density ≥ 0.10 and at least two times the value of control wells containing bicarbonate buffer only.

RSV neutralizing activity in serum. An MNA for group A RSV was carried out according to published methods [Falsey and Walsh, 1996]. Briefly, serum dilutions (1:50–1:12,800) were incubated in 96-well microtiter plates with 50–75 plaque-forming units (pfu) of Long strain RSV for 30 min with or without a 1:10 dilution of guinea pig complement. HEp-2 cells were added to the wells and the plates incubated for 3–4 days in 5% CO_2 at 35°C. The plates were washed and fixed and RSV antigen production quantitated by an EIA using an F-specific MAb. Titers were defined as the serum dilution in which color development was reduced by 50%.

Nutritional assays. Serum albumin was measured by the Rochester General Hospital Clinical Laboratories using standard methodology. Vitamin A, E, and C assays were performed according to published methods [Omaye et al., 1979; Frieden et al., 1992]. B12 was measured using the MAGIC vitamin B12 radioassay (Ciba Corning Immunochemistries, Norwood, MA).

Statistics

Multiple comparisons were made using one-way analysis of variance (ANOVA) and the Tukey–Kramer multiple comparison test. The variability among titers in different groups was assessed using the Fligner and Killeen test [Conover and Johnson, 1981].

RESULTS

Clinical Characteristics

One hundred forty-six subjects were enrolled in the cross-sectional study: 41 young, 56 healthy elderly, and

TABLE I. Clinical and Nutritional Characteristics of Subjects

Characteristic	Young (N = 41)	Healthy elderly (N = 56)	Frail elderly (N = 49)
Mean age (years)	35 ± 7	72 ± 5	79 ± 9
Male:Female	10:31	21:35	19:30
IADL[f]	0	.12 ± .9	9.81 ± 2.2[a]
ADL[f]	0	.02 ± .13	4.6 ± 3.0[a]
≥4 Chronic conditions	0	1 (2%)	41 (84%)[a]
Vitamin A[e]	51.5 ± 13.5	63.9 ± 14.6[b]	59.1 ± 23.4
Vitamin C[e]	0.85 ± 0.33	0.9 ± 0.3	0.87 ± .36
Vitamin E[e]	1136 ± 381[c]	1725 ± 525[c]	1448 ± 418[c]
Vitamin B12	459 ± 156	427 ± 205	578 ± 377[d]
Albumin	4.52 ± .29	4.10 ± .26	3.94 ± .37[a]

IADL, instrumental activities of daily living; ADL, activities of daily living.
[a]Frail vs. healthy elderly or young, $P < .001$.
[b]Healthy elderly vs. young, $P < .05$.
[c]Young vs. healthy vs. frail elderly, $P < .05$.
[d]Frail vs. healthy elderly, $P < .05$.
[e]Data missing for one healthy elderly subject.
[f]ADL and IADL are standard measures of functional ability to perform routine tasks such as dressing, walking, eating, etc. A score of 0 = no disability, 12 = complete disability.

49 frail elderly. The clinical characteristics are shown in Table I. The mean age of the young group was 35 years, all of whom were completely independent; most had no underlying medical conditions. The healthy elderly had significantly more chronic conditions than did the young, but no significant differences were noted in their functional status. The mean age of the frail elderly was slightly higher than the healthy elderly (79 ± 9 years vs. 72 ± 5 years, P = NS); however, there were striking differences in functional status and the number of chronic conditions. Markers of nutritional status for each group are displayed in Table I. Although a few statistically significant differences among the groups were found, the mean vitamin levels for the elderly groups were higher than the young and very few individuals were actually vitamin deficient. The percent of individuals taking regular vitamin supplements was slightly higher in the older groups, but the difference was not statistically significant (data not shown). Serum albumin was significantly lower in both elderly groups compared with the young subjects.

Baseline RSV Humoral Immune Function

In general, mean RSV antibody levels in the older subjects were higher than in the young healthy volunteers. Serum IgG titers measured by EIA for all three RSV antigens were significantly higher in the frail elderly compared with the young group, and the F and Gb titers were significantly higher than in the healthy elderly (Table II). There was no difference in the mean EIA titers between the young and healthy elderly. The mean RSV MNA titers for all three groups were similar (Table II). In addition to higher mean EIA titers in the frail elderly, the individual titers showed greater diversity of the EIA-F titers (P = .013) when compared with the young and healthy elderly (Fig. 1A). Less variation was noted in MNA titers, with most of the neutralizing titers (log2) in each group falling between 9 and 13 (Fig. 1B). The percent of subjects with MNA titers ≤ 9.00 was highest in the healthy elderly at 20%, compared with 12% in the frail and 17% in the young. The higher EIA titers (i.e., binding antibody) measured in the frail elderly did not result in higher neutralizing activity, which suggests the presence of higher levels of non-neutralizing antibody. This can be expressed as the ratio of EIA-F/MNA. This ratio was significantly higher in the frail group compared to the healthy elderly and young (Table II). There was no significant correlation of RSV EIA or neutralization titers and any of the nutritional indices measured.

TABLE II. RSV Immune Function

	Young (N = 41)	Healthy elderly (N = 56)	Frail elderly (N = 49)
EIA-F	15.1 ± 1.4	15.4 ± 1.4	16.6 ± 2.0*
EIA-Ga	14.4 ± 1.3	14.8 ± 1.2	15.1 ± 1.6**
EIA-Gb	14.4 ± 1.2	14.5 ± 1.4	15.2 ± 1.4*
MNA	10.5 ± 1.1	10.5 ± 1.5	10.9 ± 1.6
F/MNA ratio	4.6 ± 1.3	4.8 ± 1.7	5.7 ± 2.0*

RSV, respiratory syncytial virus; EIA, enzyme immunoassay; MNA, microneutralization assay; F, RSV fusion protein.
All titers are expressed as $\log_2$. F, Ga, Gb are IgG titers to specific RSV proteins as measured by EIA. MNA is the neutralizing titer to long-strain RSV.
*$P < .05$ frail vs. both the healthy elderly and the young.
**$P < .05$ frail vs. young.

A subset of 18 persons in each group had neutralization assays performed with and without complement in the assay. The mean MNA titer with complement versus without was nearly identical in all three groups (young, 10.3 ± 1.1 vs. 10.25 ± 1.9; healthy elderly, 10.22 ± 1.1 vs. 10.10 ± 1.1, frail elderly, 10.53 ± 1.8 vs. 10.46 ± 1.5).

Humoral Response to RSV Infection

Twenty-eight frail elderly and 11 young staff at the daycare had an RSV infection during the surveillance study. Of these, 12 were culture positive and 27 were seropositive only. Baseline and convalescent titers for the frail and young are displayed in Table III. Consis-

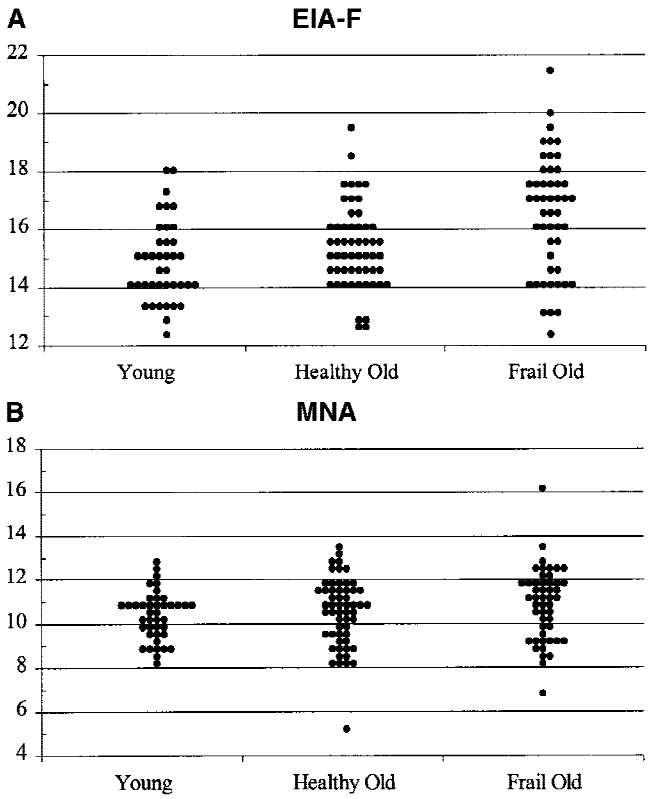

Fig. 1. Distribution of individuals titers for each group of subjects expressed in log 2. **(A)** Enzyme immunoassay-F (EIA-F) titers. **(B)** Microneutralization assay (MNA) titers.

TABLE III. Response to Natural Infection

Titer	Young (N = 11)	Frail elderly (N = 28)
EIA-F		
Pre	13.6 ± 2.0	14.4 ± 1.7
Post	16.4 ± 1.4	18.2 ± 1.8
Rise F	2.8 ± 1.7	3.8 ± 2.3
Range	(1.5–7.0)	(−1–8.5)
EIA-Ga		
Pre	12.0 ± 1.5	12.9 ± 1.8
Post	14.1 ± 1.5	15.6 ± 2.0
Rise	2.2 ± 1.6	2.7 ± 1.9
Range	(.5–3.5)	(−1–7.0)
EIA-Gb		
Pre	12.6 ± 1.9	13.6 ± 1.7
Post	15.0 ± 1.3	16.6 ± 1.6
Rise	2.4 ± 1.2	3.0 ± 1.7
Range	(0–4.5)	(1–7.5)
MNA		
Pre	10.7 ± 1.0	10.8 ± 1.3
Post	13.0 ± 1.3	13.7 ± 1.3
Rise	2.3 ± 1.4	2.9 ± 1.3
Range	(.5–3.5)	(1–6.0)
F Rise/MNA Rise Ratio	0.55 ± 2.1	0.77 ± 1.6

EIA, enzyme immunoassay; F, RSV fusion protein; MNA, microneutralization assay.

tent with the findings in the cross-sectional study, the frail elderly group had higher baseline EIA titers to all three antigens and similar MNA titers when compared with the young. The magnitude of the immune response as measured by EIA or MNA was slightly greater in the frail elderly compared with the young. A greater percentage of elderly had an antibody response to each of the antigens. Fifty percent of the elderly group had a ≥fourfold rise to all three antigens compared with only 18% for the young group. This difference appeared to be due to a better response to the G protein. Of the older infected subjects, 64% and 82% had ≥fourfold rise in titers to Ga and Gb, respectively, compared with 36% and 64%, respectively, of the young.

DISCUSSION

In contrast to infants, there is little information about immunity to RSV and no information on disease pathogenesis in the elderly. The severe clinical manifestations of RSV in the aged may be due to frailty of the host, global immunosenescence, or an age-related decline in RSV-specific immune functions. Immune dysregulation has been described in older persons, with age-related changes most clearly demonstrated in cellular immunity [Powers, 1992; Adler et al., 1994; Abraham and Davis, 1996]. Although less dramatic, aging also effects humoral immunity [Weksler, 1995].

Several reports indicate that all older adults have measurable RSV-specific IgG in their serum and that most infected individuals will develop a ≥fourfold increase in IgG EIA [Agius et al., 1990; Falsey and Walsh, 1992]. Older persons appear to mount a variable IgM response, with 11–81% of elderly having RSV IgM detected in the serum during acute infection [Vikerfors et al., 1988; Agius et al., 1990]. This study is the first to examine if older persons have a qualitative defect in RSV antibody by comparing baseline RSV neutralizing titers and the response to acute infection to young subjects.

The results of this study suggest that the increased morbidity and mortality observed in older persons with RSV infection is not due to a major defect in the humoral immune system. Despite significant differences in the age and functional status of subjects, no decrease in quantitative or qualitative measures of RSV serum antibody were found. In addition, no differences in complement-enhanced neutralizing titers were seen to suggest age-related differences in IgG isotypes. In contrast to the results of our previous small sample, the healthy elderly in this study did not have lower baseline RSV antibody titers than the young [Falsey, 1998]. This observation is presumably due to the larger sample size in the current report. Somewhat surprisingly, the oldest and frailest group was found to have the highest baseline RSV titers to the F, Ga, and Gb proteins by EIA. One explanation for this finding is that rates of acute respiratory infections are high in senior daycare centers and recent RSV infection may have boosted antibody levels [Falsey et al., 1995b]. However, MNA titers were not significantly higher in the frail group despite postulated recent reinfections. It is possible that neutralizing activity during acute infec-

tion is in part IgM mediated and is not as durable as antibody detected by EIA.

The findings of higher EIA titers without a similar elevation in the neutralizing titers in the frail group also raises the concern that immune dysregulation, manifest as excess production of non-neutralizing antibody, may occur in chronically ill older persons. Animal data suggest that high levels of EIA-F antibody with low neutralizing activity is associated with increased pathology in the lungs of infected rodents [Murphy et al., 1990; Connors et al., 1992]. Despite baseline differences in RSV antibody titers, the frail elderly showed a robust neutralizing and EIA antibody response that was slightly greater than the young. Seventy-nine percent of the older subjects had ≥fourfold increases in neutralizing titers compared with 64% of the young. Although the frail elderly did produce both a vigorous EIA and MNA response to infection, they did have a greater EIA-F rise and a higher F/MNA ratio than did the young. Therefore, it is possible that although the humoral immune response of the elderly appears to be basically intact, there may be some mild dysregulation of antibody production.

Rates of acute respiratory tract infections decline with increasing age in elderly persons living in the community [Monto and Ullman, 1974]. This decline in infections may reflect partial immunity but also may be due to a lack of exposure in individuals who are no longer in the workplace or exposed frequently to small children. Therefore, it is not unexpected that the healthy elderly had the highest percentage of individuals with "low" titers (<9.00). In a case-control study in frail elderly, we found that low serum neutralizing antibody titers were associated with a higher RSV infection rate [Falsey and Walsh, 1997a]. Cases and controls had a wide range of titers similar to the results of this study. Subjects with neutralizing titers in the lowest third had an infection rate of 67% compared with 18% in those with titers in the highest third. This finding suggests that elderly persons with titers in the lowest third of neutralizing titers may be at risk for infection and potentially could benefit from vaccination. Previous work with PFP-2, a candidate RSV vaccine, shows that response rates correlate with low serum neutralizing titers [Falsey and Walsh, 1996, 1997b].

In conclusion, baseline RSV antibody levels in the elderly likely reflect the time elapsed since last infection rather than age or functional status. In addition, the humoral response to RSV infection of older persons both healthy and frail appears to be relatively intact. It is therefore reasonable to expect that if an effective RSV vaccine can be developed, older persons should be capable of responding. The role of mucosal and cellular immunity in risk of infection, disease pathogenesis, and vaccine development for the elderly are areas requiring further study.

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